

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim 12 are requested to be canceled.

Claims 1, 5-8, and 10 are currently being amended.

Claim 14 is being added.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. No new matter is being introduced.

After amending the claims as set forth above, claims 1-11 and 13-14 are now pending in this application.

I. Claim rejections under 35 U.S.C. §103

The PTO rejected claims 1-11 and 13 under 35 U.S.C. §103 (a) as being unpatentable over Cho *et al* in view of Jensen *et al*. Office Action at pages 2-5. According to the PTO, Cho and Jensen suggested the claimed compound by motivating one skilled in the art to modify R position of podophyllotoxin with a maleimide compound, even though the maleimide compounds in Jensen are separate molecules and not attached to an amine at the requisite position as described in Cho. The PTO reasons that the motivation comes from the expectation of success from the combination of the two compounds, both of which have antitumor activity. However, because neither of the cited references suggests such a putative expectation of success from an altered structure, the references fail to support the rejections. Applicants therefore respectfully traverse on the ground that the PTO has not establish a *prima facie* case of obviousness.

The cited references' bare disclosure of the antitumor activity of both compounds does not manifest any motivation or suggestion to combine, let alone expectation of success. Instead, Cho **teaches away** from modifying R position of podophyllotoxin with a maleimide

moiety as claimed in the present invention. Cho teaches that a positive charge at the R group position is required in order to interact with the negatively charged DNA backbone. Cho *et al* at page 1394, 2nd paragraph. In contrast, maleimides are compounds rich in negative charge known by one skilled in the art, since they bear a nitrogen, two oxygens, and three double bonds. Therefore, they do not meet the requirement of a suitable R substituent according to Cho.

Moreover, the results published by Cho in Table 1 show that an oxygen atom in β -position from the nitrogen atom does not favor the formation of the protein-DNA complex. For example, compound 15 exhibits a complex formation value of 243 whereas compound 18 has a complex formation value of 4 only. This trend is likewise observed when comparing compounds 33 and 40 with 35 and 11.

Furthermore, the antitumor activities obtained with the compounds of the present invention go far beyond what would have been expected for a podophyllotoxin derivative, with a T/C value over 575%, and above all, 50% of surviving animals at day 60 in the case of P388 leukemia. A549 similarly showed unexpected activity in lung carcinoma, with a T/C value of 225%. Specification at page 34.

For the reasons set forth above, the cited references do not support a *prima facie* case of obviousness. Accordingly, Applicants respectfully request the reconsideration and withdrawal of this ground for rejection.

II. Claim rejections under 35 U.S.C. §112, first paragraph

The PTO rejected claims 1-11 and 13 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. According to the PTO, the specification does not describe or make reference as to how to make the starting material to enable one skilled in the art to make or use the present invention. Applicants respectfully traverse on the ground that one skilled in the art can practice the present invention without undue experimentation with guidance provided by the specification coupled with what is known in the art.

The synthesis of the starting material has been abundantly described in the technical literature and therefore one skilled in the art can make it without undue experimentation.

Applicants submit herewith, for the PTO's consideration, four references as exhibits to show the state of the art. They are:

Exhibit (1): Lee *et al.* J. Natural Products 1989, 52, 606-615;

Exhibit (2) Zhou XM *et al.*, J. Med. Chem. 1991, 334, 3346-3350;

Exhibit (3) Khamal *et al.* Bioorg. Med. Chem. 2003, 11, 5135-5142; and

Exhibit (4) Miyahara M *et al.* Heterocycles 1994, 39, 361-370.

Accordingly, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

III. Claim rejections under 35 U.S.C. §112, second paragraph

The PTO rejected claims 1, 5-8, and 10 under 35 U.S.C. §112, second paragraph, for being indefinite. Applicants have amended the claims to clarify the definitions of the various substituents. Accordingly, they respectfully request the reconsideration and withdrawal of this ground for rejections.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are

needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By 

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